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Importance of Corneal Angiography in Subclinical Limbitis in a Case of Atopic Keratoconjunctivitis

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Purpose: The aim of this study was to report corneal angiography features in subclinical limbitis in a patient with atopic keratoconjunctivitis.

Methods: This is a case report.

Results: A 22-year-old woman with a medical history of atopic keratoconjunctivitis was referred for bilateral corneal neovascularization with scarring. On examination, no signs of active disease were noticed at the slit lamp. Ocular surface angiography detected active corneal limbitis, showing as limbal leakage at fluorescein angiography in the early phase and leakage after indocyanine green angiography in the late phase. The patient was treated with topical corticosteroid. At follow-up, the fluorescein angiography and indocyanine green angiography no longer showed limbal leakage, whereas the slit lamp examination was unchanged.

Conclusions: Active allergic corneal limbitis may present as subclinical inflammation, with no signs of activity at the slit lamp examination. Therefore, its diagnosis can be challenging without the use of corneal angiography.

Key Words: limbitis, keratoconjunctivitis, angiography, allergic, limbus

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Atopic keratoconjunctivitis (AKC) is a chronic inflammatory disease characterized by acute exacerbations.[1] It can have systemic and ocular complications, such as eczema, blepharitis, tear dysfunction, and cataract.[2]

Corneal involvement is manifested in superficial punctate keratopathy, epithelial defects, shield ulcers, and possible corneal perforations.[3] If left untreated, complications may occur, leading to scarring, corneal vascularization, amblyopia, and reduced visual acuity.[2] These complications are not infrequent, considering that the 60% of patients affected by AKC develop corneal neovascularization (CoNV), which can eventually lead to a need for corneal transplant to improve the visual acuity.[4] Furthermore, allergic conjunctivitis represents the second most common cause of bilateral limbal stem cell deficiency (LSCD).[5]

The management of patients with AKC can be challenging because long-term use of topical corticosteroids results in side effects such as cataract. Chronic ocular surface inflammation and corneal vascularization and the proclivity for trophic epithelial defects can potentially increase the risk for corneal graft failure.

In this case report, we highlight the importance of corneal angiography in such patients to assess the state of activity of ocular surface inflammation to better tailor the therapeutic approach and monitoring.

CASE REPORT

A 22-year-old woman was referred to our hospital for bilateral CoNV with scarring. Her past medical history revealed presence of erythema nodosum and atopy because she had been diagnosed with eczema, asthma, hay fever, dust allergy, and atopic keratoconjunctivitis. Her ocular history showed negative results for herpetic keratouveitis, trauma, infections, or use of contact lenses. She was on topical tacrolimus 0.03% ointment twice daily (Protopic; Leo Laboratories Limited, Maidenhead, UK), oral antihistaminic drug (cetirizine 10 mg once daily), and occasional courses of olopatadine 0.1% (Opatanol; Norvartis Pharmaceuticals UK Ltd, London, UK) and prednisolone 1% (Pred Forte; Allergan Ltd, Marlow, UK) eye drops, which have been used discontinuously in the past.

On examination, the best-corrected visual acuity was 20/40 in the right eye (RE) and less than 20/200 in the left eye (LE), and the intraocular pressure was 18 mm Hg in the RE and 8 mm Hg in the LE.

At slit lamp examination, the AKC was inactive according to the 4-point composite score, proposed in previous studies.[6,7] Indeed, the patient complained only of nonspecific discomfort and occasional itchiness. No mucoid discharge, bulbar conjunctiva hyperemia, or punctate keratitis was present.

Of note was the bilateral corneal pannus with superficial and deep CoNV and scarring in both eyes. In the RE, major vessels came from the temporal area of the cornea, reaching the pupil center. In the

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LE, whole cornea was involved, with a 360-degree CoNV, prominent especially from the inferior side (Figs. 1A, B). However, the state of activity of the corneal pannus was uncertain because no signs of edema and leakage were noticeable at biomicroscopy.

To better estimate the possible presence of subclinical ocular surface inflammation activity, the CoNV status, and to plan suitable therapy and monitoring, an anterior segment fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed. The scanning laser ophthalmoscope (HRA2; Heidelberg Engineering, Heidelberg, Germany) was used to perform the angiography.

The FA showed limbal leakage at the early phase (~1 minute after injection) and ICGA dye leakage in the late phase (5–10 minutes after the injection), more pronounced in the left eye and in the superior hemicornea (Figs. 2A, B). These findings highlighted subclinical inflammation of the limbus. Late leakage of corneal vessels was also noticed at FA and ICGA.

The patient was recommended to continue treatment with tacrolimus 0.03% ointment twice daily and in both eyes to start topical dexamethasone 0.1% (Dexafree; Thea Pharmaceuticals Ltd, Newcastle Under Lyme, UK) 6 times per day and topical olopatadine 0.1% (Opatanol; Norvartis Pharmaceuticals UK Ltd, London, UK), twice daily, for 8 weeks. At review, the patient reported to feeling better, with less ocular discomfort. The best-corrected visual acuity remained stable, and at slit lamp, the ocular surface appeared unchanged (Figs. 3A, B). Limbal FA and ICGA leakage was no longer present, proving the efficacy of the treatment (Figs. 4A, B).

DISCUSSION

Although the correlation between AKC and LSCD has already been documented,[5] this case report highlighted the importance of anterior angiography to diagnose subclinical inflammation of the limbus. Persistent subclinical inflammation has already been described as a cause of harm for limbal stem cells, possibly leading to deficiency.[8]

Regarding the relationship between active corneal limbitis and AKC, it is still limited to a single series of 3 case reports,[9] in which the limbus was the only structure involved in 3 patients with symptoms of ocular allergy and clinical signs seen at slit lamp.

In this described case, the patient did not show any signs of active limbitis at slit lamp examination because she presented just bilateral corneal pannus, wider in the left eye. Subsequently, it could have been hypothesized that she already had irreversible LSCD, whereas the anterior angiography detected, instead, active and, possibly, reversible limbitis.

The easiest, fastest, and most common way to evaluate the ocular surface and the corneal limbus is through biomicroscopy or using color images. These methods are reliable in cases of active inflammatory disease, where the related signs and symptoms are evident, for example, ocular discomfort, conjunctival hyperemia and chemosis, and corneal involvement of various degrees.[6,7,10]

In cases of subclinical inflammation, ocular signs may be mild and generic and symptoms reported by patients. In our case, the patient complained about generic, not well-specified discomfort and occasional itching. Despite the lack of clear signs of inflammation and symptoms, there was, however, an active limbitis, discovered in our case only using the angiography.

In view of the abovementioned reasons, the slit lamp examination alone and color images may not be suitable for a correct evaluation, considering also intraobserver and interobserver variability and reproducibility.[11]

Instead, a more accurate method to grade the inflammatory activity of the ocular surface is the combined use of FA and ICGA. These methods can delineate blood vessels, providing also a wide range of information, such as vascular leakage, area, origin, diameter, and tortuosity,[12–15] and have been accepted for better evaluation and management of AKC.[7]

It should be noted that FA and ICGA are not the only diagnostic tests capable of detecting the inflammation status of the ocular surface, which can be spotted by impression cytology and confocal microscopy as well.[16–18] Angiography can be used in conjunction with impression cytology and confocal microscopy to confirm and better locate the site of inflammation, especially in patients without clear signs of inflammation or active CoNV.

Our patient presented with both FA and ICGA leakage in both eyes, indicating an active inflammation of the limbus, which left untreated can exacerbate LSCD. Her existing therapy of topical periocular ointment twice daily of 0.03% tacrolimus and oral 10 mg of cetirizine once daily was not appropriate to control the inflammation, probably because she was not administering topical antihistaminic or steroid on a daily basis.

After these findings, a course of topical preservative-free topical dexamethasone was commenced, aiming to reduce the subclinical inflammation and safeguarding the limbus. The choice of preservative free was to try and avoid any further source of irritation for the ocular surface,[19] and the dexamethasone was preferred to others in view of its long-

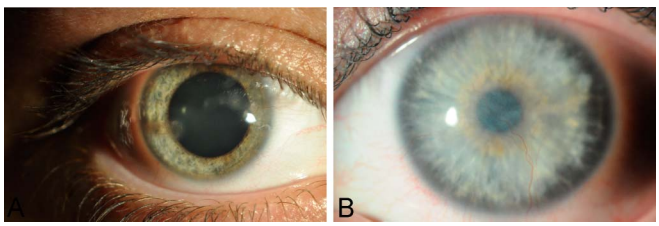

FIGURE 1. A, Anterior segment photograph of the RE at baseline. B, Anterior segment photograph of the LE at baseline.

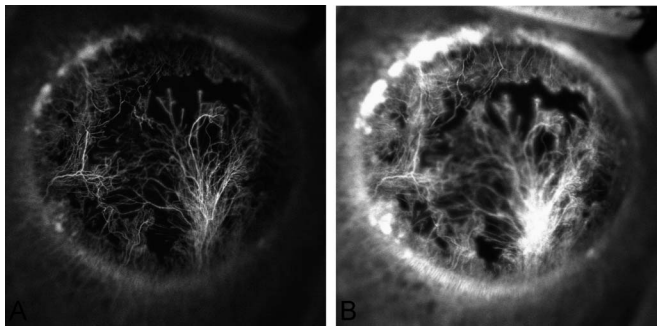

FIGURE 2. A, Early leakage of the LE at fluorescein angiography. B, Late leakage of the LE at fluorescein angiography.

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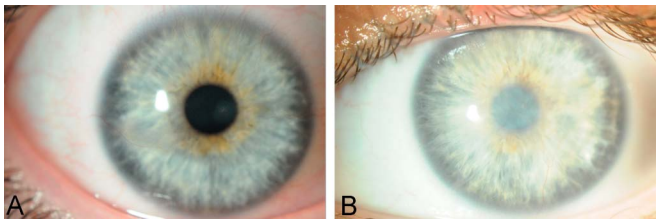

FIGURE 3. A, Anterior segment photograph of the RE at the follow-up. B, Anterior segment photograph of the LE at the follow-up.

lasting antiinflammatory effect,[20] and patient's negative history of glaucoma or high intraocular pressure.

Focusing on the mismatch between slit lamp and angiography findings, it was not possible to exclude that the leakage at limbus in both eyes may be related to lymphangiogenesis (LA) rather than hemangiogenesis. Indeed, others have shown that allergic eye disease promoted the growth of lymphatic vessels in the cornea,[21] and corneal LA seems to be related to the degree of CoNV and to regress earlier than CoNV.[22] Subsequently, because the patient presented with advanced bilateral CoNV, and in view of the response to topical treatment, the lack of leakage at follow-up angiography may be explained by regression of limbar lymphatic vessels, meditated by topical corticosteroids, which suppressed the inflammatory-related corneal LA.[23]

Limitations of our case report are the absence of further diagnostic tests to evaluate the ocular surface inflammation, such as impression cytology and confocal microscopy, which require, however, additional resources that are less widespread in routine ophthalmic clinics than angiography. In addition, the response to the therapy could have been evaluated with change of the corneal central thickness.[24]

Although rare, there are some risks associated with FA and ICGA. We recommend reserving their use for selected patients who complain of symptoms without clear signs of active CoNV or present with limbar inflammation at slit lamp. Further comparative studies are needed to evaluate the implementation of FA and ICGA in the aforementioned patients.

In conclusion, our observations showed that in eyes with chronic disease, such as allergic conjunctivitis, and concurrent subclinical inflammation, with no appreciable signs of active disease at slit lamp examination, further angiography procedures are necessary to better evaluate and manage the health of ocular surface.

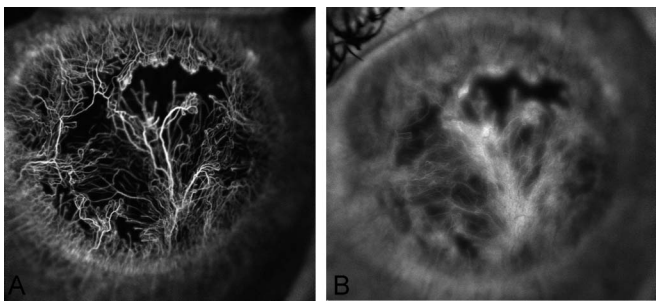

FIGURE 4. A, LE at fluorescein angiography in the early phase. B, LE at fluorescein angiography in the late phase.

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